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10/587,184	08/31/2006	Pierre J-M. Riviere	15041.0006USWO	6577

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MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,184	RIVIERE ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-23* is/are pending in the application.

4a) Of the above claim(s) *5 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-12 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: seq. alignment, Drug data sheet , FORTEO webpage.

DETAILED ACTION

Response to Amendment

Applicant's amendment of the claims filed on 27 May 2009 has been entered. Applicant's remarks filed 22 December 2008 and 27 May 2009 are acknowledged.

Election/Restrictions

In the Office Action mailed on 30 April 2008, Applicant was required to elect a single invention from Group I (claims 1-12, drawn to a method of ameoliorating symptoms associated with growth of bone cancer comprising administering a PTH receptor agonist) and Group II (claims 13-20, drawn to a medicament thereof). In the reply received on 28 May 2008, Applicant elected Group I. A Non-Final Office Action on the merits was mailed on 20 August 2008, in which claims 1-12 were examined. In the response received on 22 December 2008, Applicant has amended the claims to recite multiple amino acid sequences (for example, the generic sequences in claim 1 and SEQ ID NOs: 1-43 in claim 23). The Examiner sent out a second Requirement for Restrictions/Election on 27 April 2009, and requested election of a single species for a PTH receptor agonist, which: (1) comprises an activation domain (with amino acid sequence defined) and a receptor binding domain (with amino acid sequence defined); and (2) is selected from the group consisting of: SEQ ID NO: 1 through SEQ ID NO: 43. In the reply received on 27 May 2009, Applicant elected, with traverse, the species of: (1) a PTH receptor agonist which comprises an activation domain comprising an amino acid sequence of SVSEIQL (aa 1-7 of SEQ ID NO: 1) and a receptor binding domain

comprising an amino acid sequence of LRKKLQDVHNF (aa 24-34 of SEQ ID NO: 1); and (2) a PTH receptor agonist of SEQ ID NO: 1.

The traversal is on the ground that the species of claim 1 do form a single general inventive concept under PCT Rule 13.1 because the claimed sequences have the single inventive concept of a PTH receptor agonist effective to reduce pain. Applicant argues that claim 1 recites a PTH receptor agonist effective to reduce pain comprising at least 25 amino acids and having identified activation and receptor binding domains. Applicant also argues that it would not be unduly burdensome to search and examine all the claims.

Applicant's arguments have been fully considered but have not been found to be persuasive. The species are independent or distinct because each of the PTH receptor agonists has a unique structure as evidenced by a specific amino acid sequence for the molecule. These different amino acid sequences represent the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

The requirement is still deemed proper and is therefore made FINAL.

Claim 2 is cancelled. Claims 1 and 3-23 are pending. Claims 13-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 1, 3-12 and 21-23 are under examination to the extent they read on the elected species as indicated above. Since the PTH receptor agonists Applicant elected in the species election is a PTH or an analogue thereof, claim 5, which is directed to PTHrP or an analogue thereof, is therefore withdrawn from further consideration as being drawn to a nonelected species. Claims 1, 3, 4, 6-12 and 21-23 read on the elected species, and are under examination.

Sequence Rules Compliance

Applicant has amended claim 22 to add sequence identifier (i.e., SEQ ID NO) for the recites sequences. The instant application is now in compliant with the sequence rules, 37 CFR 1.821-1,825.

Specification

The objection to the specification for not containing, as a first paragraph, a claim to benefit of priority to any application is withdrawn in response to Applicant's amendment of the specification filed 22 December 2008.

The objection to the specification for having a title inconsistent to that in the Application Data Sheet is withdrawn in response to Applicant's amendment of the specification filed 22 December 2008.

Claim Objections/Rejections Withdrawn

The rejection of claims 1-3 and 5-11 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the genus of PTH receptor agonists, is withdrawn in response to Applicant's amendment of the claims to recite structurally defined PTH receptor agonists, and in view of Applicant's species election for the PTH receptor agonists to be examined.

The objections to claims 1 and 7 for typographical errors are withdrawn in response to Applicant's amendments of the claims.

Claim Objections/Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The amended and newly added claims 1, 3, 4, 6, 7, 10-12 and 21-23 are rejected under 35 U.S.C. 102(b), as being anticipated by Hock (WO 01/21198, International Publication Date 29 March 2001), for reasons set forth in the previous office action and the following.

In the response received on 22 December 2008, Applicant argues that the presently claimed invention is a method for ameliorating pain associated with the growth of bone metastasized cancer or bone-originated cancer, and Hock discloses a method of reducing the risk of cancer in a patient who is susceptible to acquiring cancer. Applicant argues that treating pain is not the same as preventing carcinogenesis.

Applicant argues that Hock teaches the use of parathyroid hormone for reducing the risk of developing cancer in patients who do not have cancer but are at risk of developing cancer. Applicant argues that in Hock's example, patients were selected based on their likelihood of developing cancer, not on whether they were already suffering from cancer; and there were no criteria for evaluation based on a decrease in the size or number of tumors. Applicant argues that by contrast, the presently claimed invention is limited to patients who are suffering from bone metastasized cancer or bone-originated cancer.

Applicant also argues that the Hock specification fails to provide any support for the presently claimed invention, and dos not enable a skilled artisan to practice the administration of PTH on patients suffering from bone metastasized cancer or bone-originated cancer to reduce pain. Applicant argues that the dosages disclosed in the example are directed to the administration of PTH to patients without cancer.

Applicant further argues that Hock does not inherently discloses the amount of PTH effective to reduce pain, because reducing pain in patients suffering from bone metastasized cancer or bone-originated cancer cannot be inherent in Hock's method of reducing cancer in patients who are susceptible to acquiring cancer, and the subjects of the treatment are different. Applicant argues that the Hock specification does not provide dosage or administration schedules directed to the reduction in pain in a patient with symptoms associated with bone metastasized cancer or bone-originated cancer; instead, Hock has determined an acceptable dosage range for hPTH (1-34) for reducing the risk of cancer. Applicant argues that the reduction in pain limitation of the presently

claimed invention is not inherent within the Hock specification because it is not necessarily present nor would it be recognized by a person of ordinary skill in the art.

Applicant's argument has been fully considered but has not been found to be persuasive.

First, the presently claimed invention is directed to "a method of **ameliorating symptoms** associated with the growth of bone metastasized cancer or bone-originated cancer, comprising administering to an individual in need thereof a medicament comprising **an amount of PTH receptor agonist effective to reduce pain**" (emphasis added), contrary to Applicant's argument that the presently claimed invention is a method for **ameliorating pain** associated with the growth of bone metastasized cancer or bone-originated cancer.

Hock teaches administering a parathyroid hormone, such as recombinant human PTH 1-34 (rhPTH(1-34), also known as teriparatide), for reducing the risk of cancer in a subject (pp. 6, lines 1-2, and lines 20-22). Human PTH 1-34 has the identical amino acid sequence as SEQ ID NO: 1 and comprises the activation domain (amino acids 1-7 of SEQ ID NO: 1) and the receptor binding domain (amino acids 24-34 of SEQ ID NO: 1) (see sequence alignment attached). Hock teaches that certain cancers, such as breast, prostate and lung cancer, can spread to bone, and that the method can ameliorate the damage from metastasis to bone, particularly when the spread to bone has caused a significant defect in the bone (pp. 8, lines 15-17). One of ordinary skill in the art would recognize that the patient population contemplated in the Hock disclosure includes those with certain cancers (e.g., breast, prostate and lung cancer) and bone-

metastasized cancer; and Hock's method can ameliorate the damage (e.g., a significant defect in the bone) from metastasis to bone. The "damage" referred by Hock is a symptom associated with the growth of bone metastasized cancer or bone-originated cancer. Thus, Hock anticipates the same patient population; i.e., the patient population in need of "ameliorating symptoms associated with the growth of bone metastasized cancer or bone-originated cancer". Furthermore, Hock explicitly teaches that the method can aid maintenance and rebuilding of the bone **in a cancer patient undergoing or at risk of metastasis or other growth of a tumor in bone**, and can reduce the risk of fracture in such bone (pp. 8, lines 26-27). Thus, Hock specifically teaches treating the cancer patients having undergoing tumors in bone.

With regard to the dosages, Hock teaches that the hormone is administered in a daily dose in the range of at least about 15-40 μg (pp. 6, lines 22-23), which anticipates the dosages as recited in claims 10 and 11. In other words, Hock teaches administering the same amount of the PTH to the same patient population. The resulting effects, e.g., reducing pain as recognized by the present inventors or ameliorating the bone damage as recognized by Hock, are all inherent properties, because the dosages (i.e., quantity) are the same.

With respect to Applicant's argument that the Hock disclosure dos not enable a skilled artisan to practice the administration of PTH on patients suffering from bone metastasized cancer or bone-originated cancer to reduce pain, as discussed above, Hock teaches each and every limitation recited in the instant claims. MPEP 2121 [R-6] states that:

> "When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP §716.07."

For the reasons given above, the rejection under 35 U.S.C. 102(b) as being anticipated by Hock is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a), as being unpatentable over Hock (WO 01/21198), in view of McKenna et al. (J. Bone Joint Surg. Am., 1966, 48:1-26), for reasons set forth in the previous office action and the following.

Applicant argues that McKenna merely discloses that pain is a symptom associated with osteogenic sarcomas but does not discuss the use of PTH receptor agonists effective to reduce pain. Applicant argues that under the brand name FORTEO®, PTH (1-34) is indicated for the treatment of osteoporosis; and the drug FORTEO® contains a warning label indicating that it should not be used in a subject that has been diagnosed with bone cancer or other cancers that have spread (metastasized) to the bones. Applicant argues that studies in rats demonstrated that PTH (1-34) (teriparatide acetate) demonstrated an increased risk of osteosarcoma or malignant

bone tumor that was dependant on dose and treatment duration. Applicant argues that FORTEO® is known to be contraindicated for individuals who are at increased risk for osteosarcoma or who have bone cancer or other cancers that have metastasized to bone. Applicant further refers to the FORTEO® website (www.forteo.com/public/login/login.jsp), which has a warning: "Do Not Use FORTEO® if you have ever been diagnosed with bone cancer or other cancers that have spread (metastasized) to the bones, have received radiation therapy involving the bones, or have certain bone diseases. Patients who have a bone disease should tell their doctor." Applicant argues that even if a combination of Hock and McKenna did meet all the elements of the presently claimed invention, a skilled artisan would not be motivated to combine the two references for at least the reasons given on the FORTEO® label, because it clearly states that PTH should not be used to treat patients that have been diagnosed with bone cancer or other cancers that have spread to the bones or that have certain bone diseases.

Applicant's argument has been fully considered but has not been found to be persuasive.

As stated previously, the disclosure of Hock teaches each and every limitation recited in the present claims, except that the individual has bone-originated cancer, e.g., sarcoma (claims 8, 9). McKenna et al. cures the deficiency and provides the nexus for using the PTH in these subjects. McKenna et al. teaches that osteogenic sarcoma patients (primary and secondary) have pathological fracture and pain (pp. 8, section "Signs and Symptoms").

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Hock, in view of the teachings by McKenna et al., to apply the PTH to osteosarcoma patients, thereby ameliorating the damage resulted from the growth of osteosarcomas. One of ordinary skill in the art would have been motivated to do so, because Hock teaches that administration of a PTH can ameliorate the damage caused by bone metastasized cancer, can aid maintenance and rebuilding of the bone, and reduce the risk of fracture in such bone; and McKenna et al. further teaches that the symptoms for both primary and secondary osteosarcoma are similar, i.e., patients develop pathological fracture and pain. Therefore, the combined teachings provide a reasonable expectation of successfully ameliorating the bone damage in these patients.

With regard to the FORTEO® (teriparatide) drug label that Applicant referred to, Applicant has not provided a copy for the document. Thus, without actually reviewing the evidence, the Examiner cannot provide a though response to this argument. However, based upon what Applicant has alleged in the remarks regarding FORTEO® and by referencing to the FORTEO® website (the webpage is attached herein), it is still not sufficient to overcome the obviousness rejection. In the "Important Safety Information" section, it states that "As part of drug testing, teriparatide, the active ingredient in FORTEO®, was given to rats for a significant part of their lifetime. In these studies, teriparatide caused some rats to develop osteosarcoma, a bone cancer.... It is not known if humans treated with FORTEO® also have a higher chance of getting osteosarcoma." This statement clearly points out that in the animal test, occurrence of

osteosarcomas resulted from administration of teriparatide for "a significant part of their lifetime". However, the drug is never intended for such a long term use. In the "Adverse Events" section, it states "using FORTEO® for more than 2 years is not recommended."

In addition, Applicant relies upon post-filing evidence as basis for arguing the obviousness rejection. The FORTEO® website, along with the "Prescription Information" located in the website (also attached herein), are all posted in 2009 by *Eli Lilly and Company*. The law under 35 U.S.C. 103(a) states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious **at the time the invention was made** to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. (Emphasis added)

The evidence cannot demonstrate the state of art "at the time the invention was made". Thus, Applicant has not provided sufficient evidence and reasoning to overcome the obviousness rejection.

Claim Objections

Claims 3 are objected to because of the following informalities:

Claims 3 uses an acronym, "PTH", without first defining what they represent in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym. It has been noted that claims 4 and 12, which depend from claim 3, recites "wherein said parathyroid hormone or an analogue thereof". Claim 3 does not recite "parathyroid hormone", instead, it uses acronym "PTH".

Claim 21 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 21 recites amino acid sequences for the activation domains that are 6 residues in-length. However, claim 1, to which claim 21 depends from, recites the activation domain comprising the amino acids sequence X1-V-S-E-X2-Q-X3, which is 7 residues in length.

Appropriate correction is required.

Conclusion

NO CLAIM IS ALLOWED.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
July 23, 2009

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646